Biomedical Optics EXPRESS

Defocus flicker of chromatic stimuli deactivates accommodation

VICTOR RODRIGUEZ-LOPEZ,[1,*] ALFONSO HERNANDEZ-POYATOS,[1] AND CARLOS DORRONSORO[1,2]

[1] *Institute of Optics, Spanish National Research Council (IO-CSIC), IO-CSIC, Serrano 121, E-28006, Madrid, Spain*
[2] *2EyesVision SL, Plaza de la Encina, 10, núcleo 3, planta 4ª, E-28760 Tres Cantos, Madrid, Spain*
[*] *victor.rl@io.cfmac.csic.es*

Abstract: Tunable lenses, optical elements able to change their optical power within milliseconds, constitute an emerging technology increasingly used in ophthalmic applications. In this study, 25 subjects looked through tunable lenses at a chromatic stimulus to evaluate the perceptual response of the human visual system to periodic changes in defocus of 0.25D of amplitude and 15 Hz of temporal frequency. These defocus changes produce flicker and chromatic distortions that change with the overall level of defocus. The task in this study was to minimize the flicker by varying the average optical power, and it was performed for different myopic and hyperopic starting points. Subjects also performed a blur-minimization task in a black-and-white stimulus of the same geometry. The flicker-minimization task is more repeatable than the blur-minimization task (standard deviations ±0.17D and ±0.49D). The time per repetition of the flicker-minimization task is only 38s. Cycloplegia severely affects the blur-minimization, but not the flicker-minimization task, confirming that defocus flicker deactivates the accommodative system. This discovery can be used to develop new methods for measuring the refractive error of the eye that does not require supervision and can potentially improve existing subjective methods in terms of accuracy, precision, and measurement time.

1. Introduction

The impact of defocus on the human visual system has been studied for decades. Defocus has important consequences in different aspects of vision, from the prescription of optical corrections to the accommodative response, among others. The emergence of new programmable technologies that can induce quick changes in defocus, like tunable lenses, allows the development of new approaches to study defocus perception and of new technologies to compensate for blur or take advantage of its presence.

One example is subjective refraction, the universal process to evaluate the refractive error of an eye, where the goal is to minimize the defocus of the letter on an eye chart by changing the lenses put in front of the eyes [1]. Traditionally, this change has been performed manually, but recent automatic phoropters use tunable lenses to allow changes in the optical power digitally, faster than a manual change, saving some time during the process [2,3]. Another example in the field of medical optics is SimVis, a visual simulator that uses tunable lenses at a speed (60 Hz) higher than the fusion frequency of the visual system to create multifocal images [4].

On the other hand, the accommodation response is another physiological process where blur is key. In fact, the presence of blur is what drives the accommodative response [5]. Besides, accommodation is an important issue during the process of refractive error evaluation, common to objective and subjective refraction techniques, especially in young populations [6]. Different strategies are followed limit its impact. Even with the fogging method traditionally used in subjective refraction, which consists of reducing gradually a high positive optical power previously induced, and later incorporated into certain objective methods, mild or higher hyperopias are

#486466 https://doi.org/10.1364/BOE.486466
Journal © 2023 Received 17 Feb 2023; revised 20 May 2023; accepted 20 May 2023; published 26 Jun 2023

Biomedical Optics EXPRESS

often missed. Cycloplegic drugs can null the influence of accommodation, although they produce other unwanted effects such as pupil dilation, visual discomfort, or photophobia.

It has been reported that the accommodation of the visual system cannot follow optical periodical changes at a speed higher than 2 Hz [7–12], although the onset time of the accommodation response have been reported to be around 200 ms [13]. In a previous study, we measured the sensitivity to defocus changes in a flicker detection task for different temporal frequencies using a black-and-white stimulus [14,15], where we reported that the maximum sensitivity occurs at around 10-15 Hz and around 0.25 D of maximum focus difference. During these measurements, subjects perceived chromatic artifacts happening in the black parts of the stimulus. We believe that these artifacts appear due to the Longitudinal Chromatic Aberration of the eye (LCA), where defocus differs depending on the wavelength and thus the perception might change for the different chromatic components. How quick defocus changes in a chromatic stimulus affect the perception and how the accommodation is impacted at these high frequencies are unknown. One hypothesis is that the accommodative system, unsuccessfully trying to follow the focus changes, varies its response erratically. Another hypothesis is that the accommodation, unable to follow those changes, stays in a “fixed” state.

Demonstrating this second hypothesis would have tremendous clinical implications because accommodation interferes with and complicate many subjective procedures. For example, in the gold standard method to evaluate the refractive error of the eye, the subjective refraction [16,17], which is probably the most frequent procedure performed in eye care clinics. The purpose of subjective refraction is to find the most suitable combination of lenses that compensates for the refractive error of an eye, producing the maximum visual acuity. As mentioned before, fogging is the most common method used to eliminate the undesirable effect of the accommodation, but increases the measurement time (around 6 minutes) and the variability (around 0.26 D) [18]. In the final steps, practitioners iteratively ask the patient about the perceived blur of a visual test (usually letters black on white letters), trying different lenses and aiming to minimize said blur. Due to the natural blur of the eye, the optical aberrations, and the resultant depth of focus, the blur-minimization task is challenging both for the patients and for the practitioners. The responses are often dubious, and the practitioners must guide the patients and interpret their subjective feedback. Overall, subjective refraction is a method that has not evolved much in the last decades and therefore any progress on the stimulus, task, or method can have important consequences.

To test the hypotheses, we induced periodic temporal defocus changes of 0.25 D of amplitude at 15 Hz (where the maximum sensitivity to defocus changes happens [15]) using a tunable lens and asked the subject to minimize the flicker perception of a chromatic stimulus by shifting the defocus change. Using a chromatic stimulus produces also an interaction with the LCA, which produces differences in the flicker perception in the different chromatic components of the stimulus. Besides, subjects also performed a task to minimize the blur of a stimulus using the same geometry of the stimulus as in the flicker-minimization task, but a black and white. The accommodation response was free in both experiments. Additionally, to compare, some subjects also performed both tasks with the accommodation paralyzed using cycloplegic drugs.

2. Methods

2.1. Temporal defocus wave and perceptual consequences

In this study, we refer to Temporal Defocus Wave (TDW) as the induction of rapid and periodic temporal changes in the optical power of an eye and producing periodic temporal changes in the focus state of the retinal image while maintaining its position and magnification [19]. In this case, the TDW was a square wave, changing periodically between only two optical powers (Fig. 1). These fast periodic changes in defocus produce periodic changes in retinal blur and therefore the visual perception of flicker in the image, which is minimum when the mean optical power of the

Biomedical Optics EXPRESS

TDW corresponds to the retinal plane. The flicker increases as the mean optical power of the TDW moves away from the retinal plane, either in the myopic or hyperopic direction.

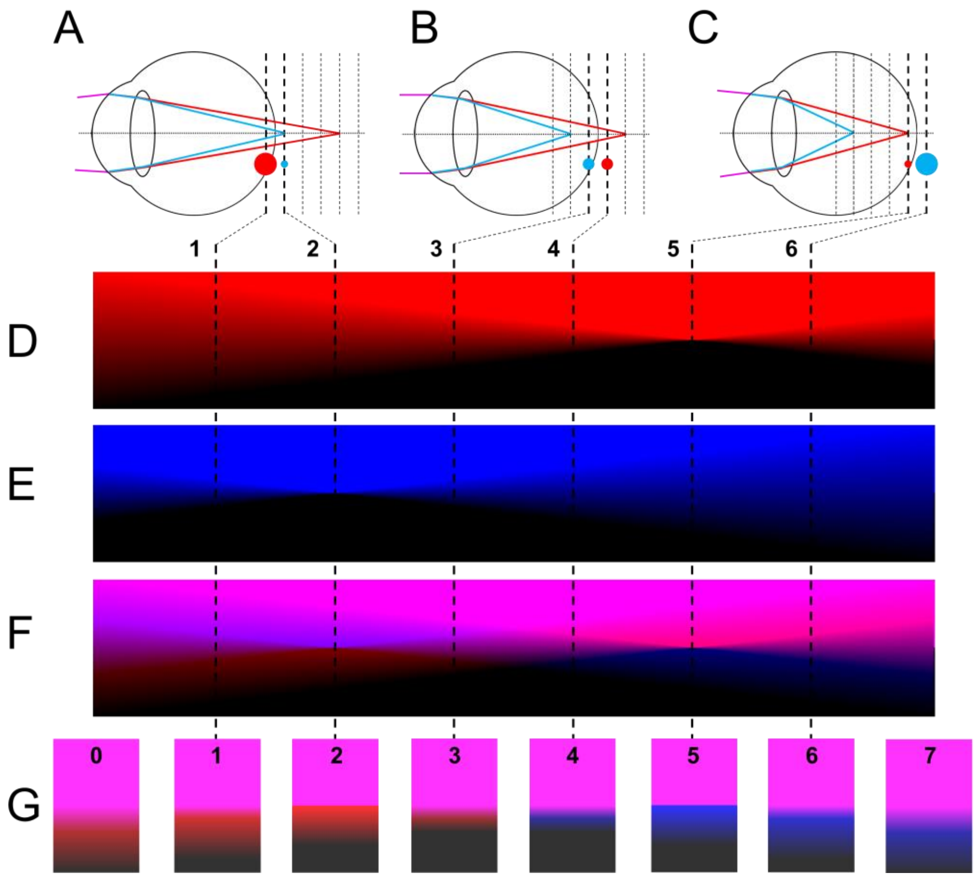

Fig. 1. Interaction of the Temporal Defocus Wave (TDW) and the Longitudinal Chromatic Aberration (LCA). The perception of the stimulus depends on the mean optical power of the TDW, which changes the focused plane in the retina. Six optical planes are represented with dashed lines (1 to 6). The two optical powers of the TDW are represented with bold dashed lines. For illustration purposes, the amplitude of the TDW was only one-third of the chromatic difference of focus between the blue and the red wavelengths. The effect will be magnified by a larger amplitude, producing a bigger change in the image of the edges. **A.** Schematic representation of the mean value of the TDW in the hyperopic side of the retina (equivalent to hyperopic refractive state). **B.** Mean value of the TDW centered with the retinal plane (equivalent to emmetropic refractive state). **C.** Mean value of the TDW in the myopic side of the retina (equivalent to myopic refractive state). **D.** Representation of the through-focus blur, induced by defocus, for a red edge. Only plane 5 is in focus. **E.** Through-focus blur for a blue edge, with plane 2 in focus. **F.** Through-focus blur for a magenta edge (red plus blue). Color distortions are different in the hyperopic and myopic sides of the retina, and in the bright and dark sides of the edges. **G.** Images corresponding to planes 1 to 6 (and to additional planes 0 and 7) of a magenta edge with high contrast and brightness represent the vision of an eye not completely adapted to a bright display. The observers perceive color distortions in the dark side of the edges: reddish tint on the hyperopic side of the retina and blueish tint on the myopic side.

Biomedical Optics EXPRESS

If a stimulus is made of different chromatic components, for example, blue and red monochromatic components and combinations of them, due to the Longitudinal Chromatic Aberration (LCA) of the eye, each monochromatic component is focused on a different axial position relative to the retina. Figure 1 describes the dynamic interactions between the LCA of the eye and the fast temporal variations of optical power induced by the TDW (Figs. 1(A), 1(B), and 1(C)). The through-focus retinal images of the edges of a stimulus are very different across chromatic components due to the LCA (as an example: red monochromatic edge through focus in Fig. 1(D); blue monochromatic edge in Fig. 1(E); magenta bi-chromatic edge -red plus blue- in Fig. 1(F)). At a given defocus, the blur is different for each chromatic component, and the different spread of light produces energy unbalances, changing the color around the edges of the stimulus (Fig. 1(G)).

Six representative through-focus planes are considered in Fig. 1, numbered 1 to 6, and shown as dashed lines in Figs. 1(A), 1(B), and 1(C). The TDW is represented by two bold dashed lines indicating the two planes of alternating foci. Figures 1(A), 1(B), and 1(C) represent three different refractive states in which the TDW has different mean optical powers with respect to the retina.

In Fig. 1(A), one of the alternating optical powers of the TDW corresponds to the blue focus of the eye (plane 2) -where the blue components of the stimulus are sharp-, and the other one places the stimulus in front of the retina (plane 1). In this situation, the best focus of the eye (in between the blue and the red foci) would lay behind the retina, on the hyperopic side (equivalent to an eye with a hyperopic refractive state). The alternation between planes 1 and 2 induced by the TDW produces (see also Visualization 1C): i) More average blur in red image components than in blue image components; ii) More flicker perception in red image components, where blur is suprathreshold in both planes 1 and 2, than in blue image components, where blur is subthreshold in plane 2 and small in plane 1, and; iii) A reddish halo within the dark side of magenta edges, and blueish halo within the bright side (Figs. 1(F) and 1 (G)) in both planes 1 and 2. The reason is that in an edge between magenta and black, the red light is spread more than the blue light. On the dark side of the magenta edge, the additional red produces a reddish halo (Fig. 1 G, planes 1 and 2).

Figure 1(C) represents the opposite situation. It could represent the same eye with more average optical power in the TDW. One of the optical powers corresponds to the red focus (plane 5), and the other one projects the stimulus behind the retina (plane 6). Because the best focus of the eye would lay in front of the retina (between the blue and the red foci), on the myopic side (equivalent to a myopic refractive state). In this other case, the observer experiences (see also Visualization 1A): i) More blur in blue than in red; ii) more flicker in blue than in red; and iii) A blueish halo within the dark side of the magenta edge (Fig. 1 (G), planes 5 and 6).

In Fig. 1(B) the eye is in focus (it could represent, again, the same eye). In this case, the eye is focused in between the blue focus -in front of the retina- and the red focus -behind the retina-. The two optical powers of the TDW correspond to planes 3 and 4, very close and at either side of the best retinal focus. The mean optical power of the TDW matches the retinal plane (equivalent to an emmetropic refractive state). Consequently (Visualization 1B): i) Blue and red components have similar amounts of blur; ii) Similar small flicker in blue and red components; and iii) Blue and red light are barely spread and the difference is hardly noticeable. The color distortions in magenta edges disappear with the fast alternation because no color dominates the other.

Blur, flicker, or color artifacts keep increasing as the TDW is more separated from the retinal plane to the myopic side (position 0) or the hyperopic side (position 7). In summary, when the eye is defocused in a TDW scheme, not only the amount of blur increases as defocus increases, but also, and more noticeably, the amount of flicker and color distortions. Even a slight residual defocus results in an increase in these effects. The color distortion is different at both sides of the focus of the eye (blueish tint of black objects if myopic defocus, reddish if hyperopic; Fig. 1 (G)).

Therefore, color artifacts not only indicate the amount of defocus, but also an unambiguous cue of the defocus sign.

2.2. Optical system

The active part of the optical system is an optotunable lens, a lens able to change its optical power in response to an electric signal. The optotunable lens used in this study is based on liquid-membrane technology (EL-10-30-TC, Optotune, Switzerland), enabling precise changes in optical power up to 100 Hz [4,20]. The TDW is produced by an optotunable lens optically conjugated with the pupil plane of the eye of the observer using a 4f-projection optical system (Fig. 2(A)). The distance from the eye pupil to the first lens is 45 mm. The distance from the optotunable lens to the stimulus is 1 meter. When inducing the TDW, the center focuses the screen, optically placing the stimulus at infinity and therefore not eliciting any accommodative response.

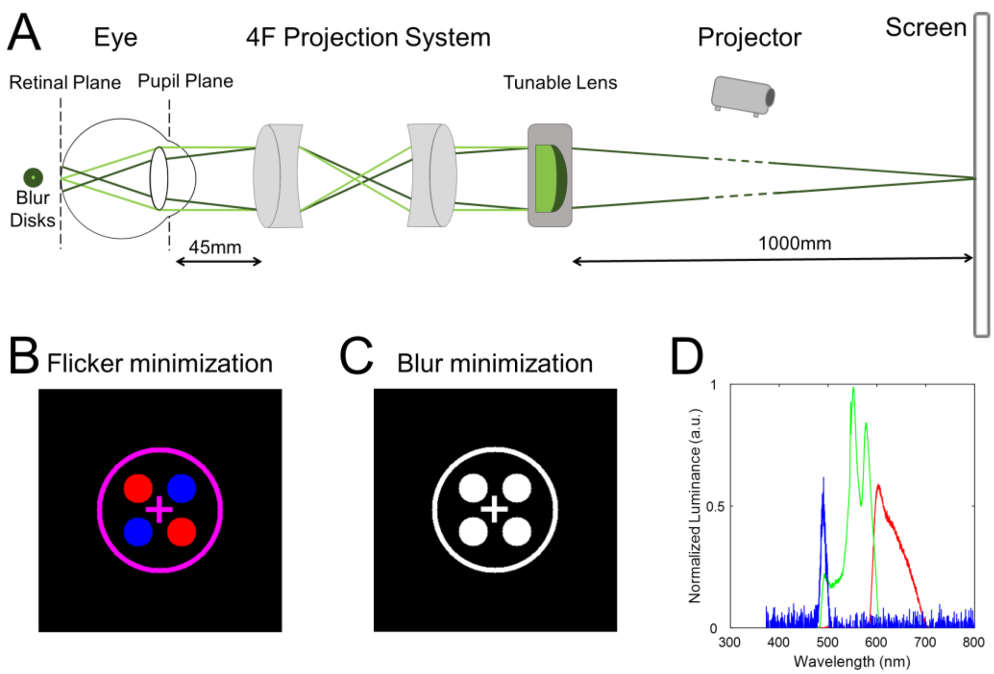

Fig. 2. Setup of the study. A. Schematic representation of the optical system of the study. It shows how inducing optical powers with the optotunable lens changes the retinal blur. The 4f optical system projects the optotunable lens on the pupil plane of the eye. In most situations, the stimulus is defocused for the observer, producing a large blur disk on the retina (dark green). In the particular situation when the optotunable lens focuses the stimulus on the retina (light green), the blur disk is minimum. With this configuration, the optical power of the optotunable lens produces defocus blur in the image, without changing the position or the magnification. The sizes and distances displayed are not proportional to the real optical system. **B.** Stimulus used to perform the flicker-minimization task See also Visualization 1 for a simulation of the appearance of the stimulus during the task. **C.** Stimulus used to perform the blur-minimization task. **D.** Spectral emission of the light source (digital light projector, DLP) for blue, green, and red components.

Biomedical Optics EXPRESS

Custom routines were programmed in MATLAB (Math-works Inc., Natick, USA) to operate the custom driver based on Arduino electronics (Arduino Nano 3; Arduino, Italy) that controls the optical power of the optotunable lens and implements the TDW. MATLAB, in combination with Psychtoolbox [21], was also used to design and present the stimuli and to perform the perceptual task.

2.3. Subjects

Twenty-five subjects, fifteen females and ten males, between the ages of 23 and 48 (29.9 ± 7.3 on average), participated in the study. All participated in Experiment 1, and five of them also in Experiment 2. No color abnormalities were found, tested with Ishihara chromatic test. All subjects had normal visual acuity (VA; ≤ 0.0 logMAR) wearing their usual correction. Far distance refraction (sphere and cylinder) based on the subject's spectacle prescription and adjusted following standard optometric procedures (fogging technique for the sphere and Jackson's Cross Cylinder for astigmatism) was set to guarantee accurate baseline refraction. Experiments were performed with the room lights switched off.

The refractive error (in spherical equivalent) ranged from -6.75 to +1.50 D (-1.62 ± 2.32 D on average) with a distribution of eight emmetropes (±0.50 D or refractive error), fourteen myopes (<-0.50 D) and three hyperopes (>+0.50 D). Subjects were free to accommodate, except in Experiment 2 where the accommodation was paralyzed using cycloplegic drugs.

A bite bar provided centration stability during the experiments. Fixation was provided by the stimuli. Only the left eye was measured. The right eye was occluded with an eyepatch. The experimental protocols were approved by the Spanish National Research Council (CSIC) Bioethical Committee and were in compliance with the Declaration of Helsinki. Written informed consent was provided by all subjects.

2.4. Experiment 1

Figure 2(B) shows the stimulus used to perform the flicker-minimization experiment. This stimulus was designed to intensify the perception of flicker and chromatic artifacts at both sides of the focus. It comprises four circles arranged like the corners of a square, alternatively red (RGB coordinates [1 0 0]) and blue ([0 0 1]), on|a black background ([0 0 0]). The diameter of the circles is 1°. They are surrounded by a thin magenta ring ([1 0 1]; 4.7° of visual angle). The stimulus also contains a magenta cross in the center, for fixation.

Visualization 1 shows a computer simulation of the interaction between the stimulus, the TDW, and the LCA of the eye, which produces flicker and chromatic distortions depending on the mean optical power of the TDW. The flicker of the blue dots is preponderant when the mean power of the TDW changes on the myopic side of the retina, while the flicker of red dots becomes more visible on the hyperopic side. Centered with the retina, flicker is minimum and similar for red and blue dots. In this stimulus, the chromatic artifacts appear in the magenta components (the fixation cross and the surrounding ring), which are shifted to blue in myopia and to red in hyperopia.

The flicker minimization task consisted of simultaneously minimizing the two concurrent effects in the image induced by the TDW: the flicker and the chromatic distortions, guided by the different color distortions. Subjects increased or decreased the mean power of the TDW using a keyboard, in coarse or fine steps of 0.25 and 0.10 D, respectively.

In the usual evaluation of the optical prescription, the goal is to minimize the blur perceived in an eyechart. In this process, accommodation plays an important role, often varying the refractive state of the eye and therefore distorting the outcome. Some strategies like fogging are used to reduce its influence. To account for the impact of accommodation, subjects also performed an unsupervised blur-minimization experiment, simulating a simplified version of the traditional subjective refraction used in clinical practice. The task of the subject was to minimize the blur (defocus) of the stimulus by changing the optical power of the optotunable lens with the keyboard (same steps of 0.25 and 0.10 D) until the stimulus was perceived as sharp. The stimuli designed for the blur-minimization task (Fig. 2(C)) is a black-and-white version of the one designed for the flicker-minimization task (Fig. 2(B)), in which magenta, blue and red colors are replaced with white ([1 1 1]).

Both tasks were performed without supervision; the experimenter explained the task and the subject performed it by themselves. The explanation preceding the experiment took about 1.5 minutes for the flicker-minimization task and 0.5 minutes for the blur-minimization task. The time elapsed between the explanation and the conclusion of the unsupervised tasks was recorded in both methods.

Subjects wore their far refraction delivered with trial glasses in a trial frame throughout the experiments. For both tasks, subjects performed 10 repetitions, each one following a staircase procedure with a different starting point: 5 of them on the myopic side, from -0.20 D to -1.00 D, and the other 5 on the hyperopic, from +0.20 D to +1.00 D. As subjects wore their far refraction, both unsupervised flicker-minimization and blur-minimization tasks measure residual refraction, i.e., deviations with respect to their far refraction. But the results, obtained from different myopic and hyperopic starting points, are representative of arbitrary refractive errors. The average and the standard deviation across all repetitions provided the residual refraction and the precision, respectively. After the measurements, VA was checked to be 0.00 logMAR or lower (i.e., better VA) with the residual refraction obtained with the flicker-minimization task.

The display was a combination of a digital light projector (DLP PJD7820HD, ViewSonic, USA) and a flat white reflecting screen. The distance from the projector to the screen was 0.4 meters, providing a sharp image with high luminance (500 cd/m^2 if set to white, according to technical specifications). The spectral emission, plotted in Fig. 2(D), shows narrow and close R and B components.

2.5. Experiment 2

In Experiment 2, five subjects (29 ± 9 years, S1-S5) also performed the same tasks (flicker-minimization and blur-minimization) using the same experimental setup as in Experiment 1, but with the accommodative response paralyzed after the instillation of cycloplegic drugs (tropicamide 1%). Measurements began 10 minutes after the instillation of the third dose in intervals of 15 minutes.

2.6. Statistical analysis

To analyze the statistical significance of the differences between the results of the different experiments, we used Wilcoxon signed-rank tests to compare the results of Experiment 1 vs 2. Additionally, to compare groups with different refractive errors (myopes, hyperopes, and emmetropes) and age (young and presbyope) we used a Mann-Whitney U-test for different sample sizes.

For each subject, we considered each repetition of the flicker-minimization and blur-minimization task as a different measurement of residual refraction. Additionally, paired t-tests and correlation coefficients were also used to compare myopic and hyperopic starting points in the flicker-minimization and blur-minimization tasks. The statistical level to achieve statistical significance was set to 5% ($p = 0.05$). MATLAB (Math-works Inc., Natick, USA) was used to perform the analysis.

3. Results

Figure 3 depicts a few representative examples of the measurements performed. Each panel shows the progress along trials (staircase) of every repetition for Subject 5 (S5), Experiments 1 and 2, and both unsupervised tasks, flicker-minimization and blur-minimization. Blue lines represent myopic starting points and red lines hyperopic starting points. The X-axis represents

Biomedical Optics EXPRESS

the trial number. The Y-axis represents the mean optical power of the TDW, in diopters, for the flicker-minimization task (examples in panels A and C) and in the optical power, in diopters, for the blur-minimization task (example in panels B and D). Subjects were compensated with their far correction while performing the experiments and therefore the result of each repetition (red or blue dots) or the average (solid black line in the center of the gray band indicating the standard deviation) represents the residual refraction (spherical equivalent) over their far correction. We identify the flicker residual refraction (FRR) for the flicker-minimization task and the blur residual refraction (BRR) for the blur-minimization task.

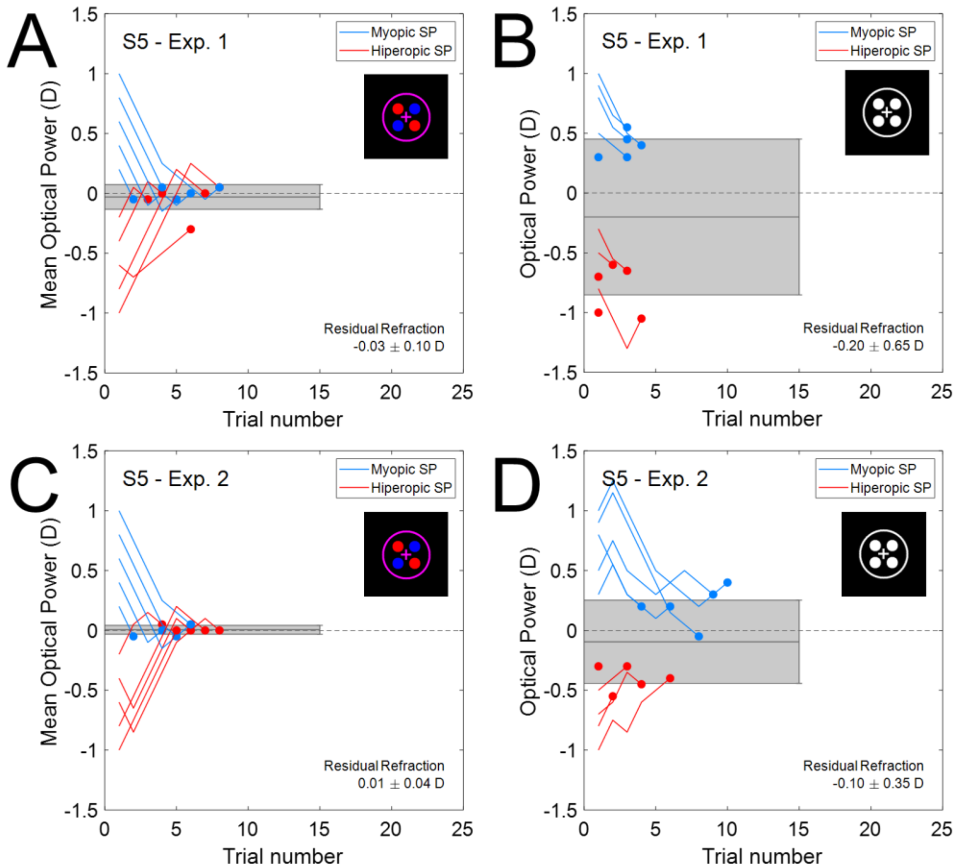

Fig. 3. Progress of the flicker-minimization and blur-minimization tasks for Subject 5 and Experiments 1 and 2. Each panel shows the progress of a subject while performing a visual task (flicker-minimization or blur minimization). Blue lines represent repetitions with myopic starting points and red lines with hyperopic starting points. The filled dot at the end of each line indicates the residual refraction for that repetition. The horizontal gray bar indicates the mean and the standard deviation of the residual refraction across repetitions. These values are indicated in the right-bottom corner of each panel. The stimulus used in each measurement is shown in the upper-right corner. **A.** Evolution of the mean optical power of the TDW (in D) versus the trial number for S5 performing the flicker-minimization task in Experiment 1. **B.** Optical power (in D) versus the trial number for the same subject (S5) and experiment while performing the blur-minimization task. **C.** Flicker-minimization task in Experiment 2 (paralyzed accommodation) for the same subject (S5). **D.** Blur-minimization task for the same subject (S5) also for Experiment 2.

Biomedical Optics EXPRESS

Figure 3(A) illustrates the flicker-minimization task for subject S5 performed in Experiment 1. All repetitions converge to a common minimization point with a standard deviation of ±0.10 D. This value is lower than the finest optical power step available in eyecare clinics (±0.25 D). Figure 3(B) shows the corresponding blur-minimization task for the same subject and experiment. In this case, there is no convergence, and the standard deviation is much higher ±0.65 D, suggesting the influence of accommodation in the outcome of the unsupervised blur-minimization task: hyperopic defocus (blue lines) can be compensated with accommodation and the subject (25 years old) perceives the stimulus instantly sharp. Due to the depth of focus of the eye, myopic defocus is also very soon perceived as sharp. Figure 3(C) shows the results of the flicker-minimization task for the same subject (S5) and Experiment 2 (paralyzed accommodation). Paralyzing the accommodation results in an even lower standard deviation (±0.04 D) with the same residual refraction (-0.03 D in Experiment 2 vs 0.01 D in Experiment 1). This suggests that, at least in this subject, accommodation was barely influencing the outcome of the flicker-minimization task in Experiment 1 (where the accommodation was free). Figure 3(D) shows the results for the blur-minimization task for S5 and accommodation paralyzed. Now, hyperopic defocus, which was accommodated when accommodation was free (Fig. 3(B)), cannot be compensated. Therefore, the standard deviation of the blur-minimization task with the accommodation paralyzed is much lower (±0.35 D). Further analysis will show the result for all the subjects measured with and without paralyzed accommodation.

The convergence of the subject to a unique result in the flicker-minimization task, regardless of the starting point for each repetition (myopic and hyperopic), is consistent across subjects and experiments and proves that the accommodative response, although functional, is not elicited during the DSR task. The quick and abrupt changes in optical power produced by the TDW seem to unfasten to some extent the accommodation mechanism from the stimulus. The flicker-minimization visual task does not require paying attention to blur and concentrates the attention of the patient on defocus flicker and chromatic distortions. Besides, the task takes place in the presence of a dynamic baseline blur that cannot be eliminated, and that seems to make

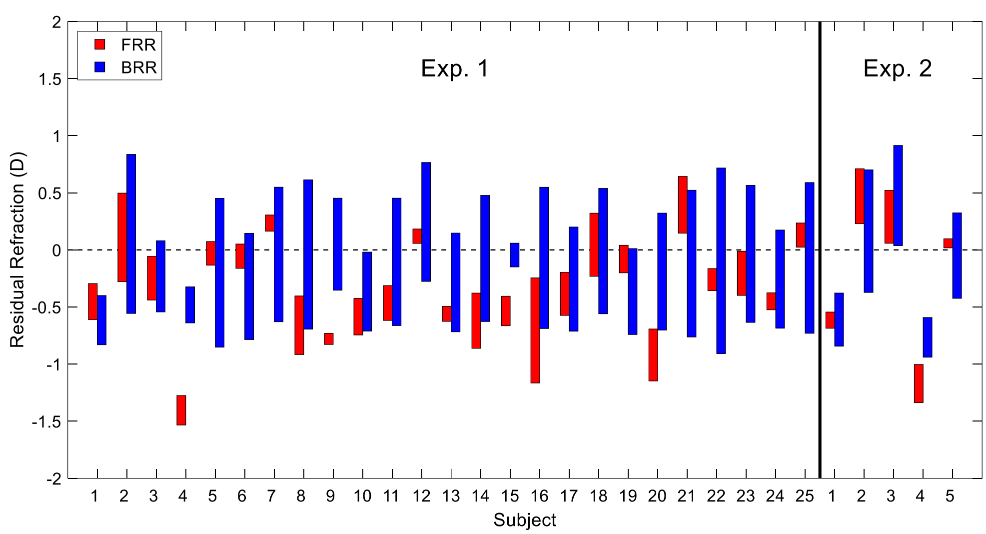

Fig. 4. Residual refraction and standard deviation for all subjects and experiments. Each bar is centered on the spherical equivalent and its length represents twice the standard deviation. Red bars correspond to the flicker-minimization task and blue bars to the blur-minimization task.

accommodation unproductive. On the contrary, as already mentioned and shown in the examples of Figs. 3(B) and 3(D), which are representative of the responses of all subjects, the unsupervised blur-minimization task is severely affected by accommodation.

Figure 4 shows the residual refraction obtained from the flicker-minimization (red) and the blur-minimization (blue) tasks, for all subjects in Experiment 1 (free accommodation) and Experiment 2 (paralyzed accommodation). The position of the bar indicates the mean across repetitions and the length indicates one standard deviation at each side of the mean. The average residual refraction obtained with the DSR task across subjects shows a myopic shift of -0.33 D. The flicker minimization method detects significant residual refractions in 80% of the subjects (measurements significantly different from zero, the far correction of the subjects, using a 0.9 significance level, i.e., red bars not touching the zero). The average residual refraction in the blur-minimization task has a lower myopic shift (-0.15 D) and captures significant residual refractions in only 12% of the subjects.

Analyzing separately the results of flicker-minimization from the two experiments, the average residual refraction and the average standard deviation across subjects are -0.33 ± 0.17 D for Experiment 1 and -0.19 ± 0.15 D for Experiment 2. Interestingly, when accommodation is paralyzed (Experiment 2), the average absolute residual error for the blur-minimization task (0.41 D) is comparable to that found in the flicker-minimization (0.36 D on average across experiments, 0.52 D in Experiment 2). For the flicker-minimization task, a paired t-test for the subjects that performed Experiments 1 and 2 reports that the differences in mean residual error were not statistically significant ($p > .05$), indicating that, in our sample, paralyzing the accommodation does not induce significant differences.

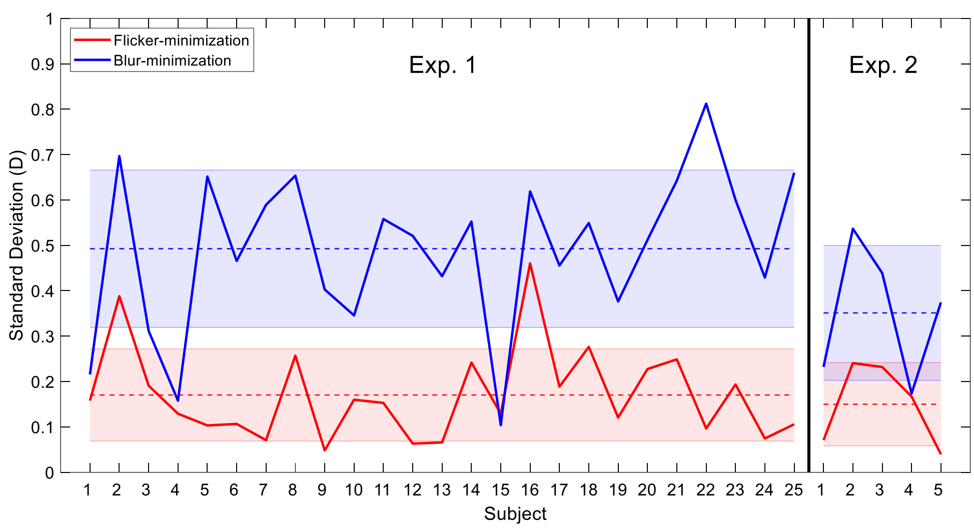

Fig. 5. Standard deviation for all subjects and experiments. Continuous lines indicate the standard deviation across repetitions for each subject. Horizontal colored bars indicate the mean and (dashed lines) the standard deviation (one to each side of the mean) across subjects of the standard deviation. In red, the flicker-minimization task, and in blue, the blur-minimization task.

Comparing the outcome from the flicker-minimization and blur-minimization tasks, we found statistical differences (paired t-test $p < .05$) in Experiment 1 with free accommodation (average of -0.33 D and -0.15 D, respectively). One might expect that, in Experiment 2, with the accommodation paralyzed, the results for flicker-minimization and blur-minimization tasks would be similar. In fact, we found that the differences are small (-0.19 D and -0.15 D for the

Biomedical Optics EXPRESS

flicker-minimization and blur-minimization tasks, respectively) and not statistically different (p > .05). Although the number of subjects in Experiment 2 is low (only 5), this result also supports that the accommodation was barely influencing the flicker-minimization task.

Figure 5 directly plots the standard deviation across repetitions for each subject and experiment, providing a closer look at the repeatability of the flicker-minimization and blur-minimization tasks. The horizontal dashed lines indicate the average standard deviation across subjects. Across the two experiments, the standard deviation for the flicker-minimization task is lower than that for the blur-minimization task in 96.7% of the subjects. The average standard deviation for the flicker-minimization task is ±0.17 D and ±0.15 D for Experiment 1 and 2, respectively, and for the blur-minimization task is ±0.49 D and ±0.35 D for Experiment 1 and 2, respectively. There is a statistically significant difference between the standard deviation of the flicker-detection task and the blur-minimization task (paired t-test $p < .05$). In fact, only one subject (S15) reported a higher standard deviation with the flicker-minimization task than with the blur-minimization task (0.13 vs. 0.10 D). These results evidence the higher repeatability (i.e., precision) of the flicker-minimization task compared to the corresponding blur-minimization task in the same conditions: Minimizing flicker and chromatic distortions happen to be more precise than judging blur.

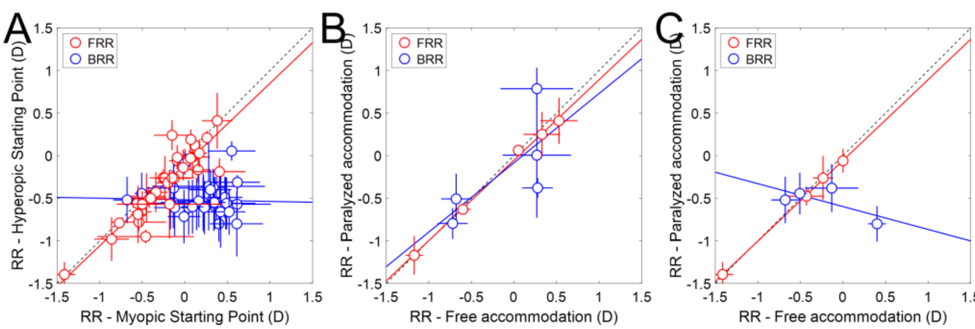

Fig. 6. Effect of accommodation in flicker-minimization and blur-minimization tasks. In these graphs, the residual refraction obtained from the average of all hyperopic starting points is plotted against the residual refraction obtained from the average of all myopic starting points for the flicker-minimization (FRR, red) and blur-minimization (BRR, blue) tasks. The error bars indicate the standard deviation across repetitions. **A.** Analysis of myopic and hyperopic starting points for all subjects in Experiment 1 (free accommodation). **B.** Analysis of myopic and hyperopic starting points for all subjects that performed Experiment 2 (paralyzed accommodation, S1-S5). **C.** Analysis of myopic and hyperopic starting points for Experiment 1 (free accommodation) for subjects that also performed Experiment 2 (S1-S5).

Figure 6(A) explores the effect of accommodation further. The results for hyperopic starting points (average of all hyperopic repetitions) are directly plotted against the results for myopic starting points (average of all myopic repetitions), both for flicker-minimization (each red symbol indicates a subject) and blur-minimization (blue symbols) tasks in Experiment 1. For flicker-minimization, on average, the residual refraction and the standard deviation obtained with myopic starting points is -0.23 ± 0.15 D and with hyperopic starting points is -0.32 ± 0.16 D, the correlation between hyperopic and myopic starting points is very high ($r = 0.90$, $p < .05$), and there is a small but significant statistical difference between them (0.09 D on average; paired t-test $p = .02$). The similarity of the results obtained with hyperopic and myopic starting points with the flicker-minimization task demonstrates that is barely affected by accommodation and that the

Biomedical Optics EXPRESS

method is very precise both for detecting small amounts of myopia and hyperopia. In contrast, for the blur-minimization task, the correlation is expectedly low ($r = -0.04$, $p = .84$) between myopic and hyperopic starting points, which provide radically different results (+0.23 ± 0.21 D and -0.52 ± 0.29 D, average difference 0.75 D, paired t-test $p < .05$). As expected, the unsupervised blur-minimization task without fogging, with a comparable stimulus and in the same set-up, is severely affected by accommodation, that not only influences repeatability but also the outcome measured.

Experiment 2 provides additional information about the effect of accommodation. Five subjects carried out the experimental session of Experiment 2 (including the flicker-minimization and the blur-minimization tasks) but under the effect of cycloplegics drugs, paralyzing their accommodation (see *Methods*). Figure 6(B) shows the results for hyperopic starting points (average of all hyperopic repetitions) are plotted against the results for myopic starting points (average of all myopic repetitions), both for flicker-minimization and blur-minimization tasks in Experiment 2. Considering the low number of subjects, the correlation shown was very high for the flicker-minimization task ($r = 0.99$, $p < .05$) and, although improves compared to Experiment 1, with free accommodation, the correlation is still low for the blur-minimization task ($r = 0.70$, $p > .05$). Figure 6(C) reinforces the results shown in Fig. 6(A), but only for subjects that performed both Experiment 1 and Experiment 2.

Figure 7 shows a scatter plot of the standard deviation across repetitions versus the average time per repetition for all subjects and experiments. We observe two clear clusters. The results for blur-minimization (blue open circles) have low measurement times but high standard deviations, while the results for the flicker-minimization (red open circles) have intermediate measurement times and low standard deviations. On average, the blur-minimization task takes 21.1 ± 12.2 seconds per repetition, and the flicker-minimization 37.7 ± 16.5 seconds per repetition (paired t-test $p < .05$). The average standard deviation for the blur-minimization task is ±0.47 ± 0.18 D (solid blue diamond) and for the flicker-minimization task is ±0.17 ± 0.10D (solid red diamond). In this plot, we also included the time per repetition and the intraoptometrist error (equivalent to the standard deviation reported for the flicker-minimization and blur-minimization tasks) of the Traditional Subjective Refraction (TSR), which takes around 6 minutes and has a variability of 0.26 D [18], indicated as a green diamond. The flicker-minimization (also the blur-minimization) task is much faster than the TSR and more precise than the TSR and, of course, than the blur-minimization task.

Finally, we investigated if the refractive error or the age of the subject influenced the flicker-minimization or the blur-minimization tasks. We divided the subjects into three groups of refractive error based on their current correction, hyperopes (>+0.50 D; 3 subjects), myopes (<-0.50 D; 14 subjects), and emmetropes (±0.50 D; 8 subjects); and into two groups, based on age, young (<45 years, 23 subjects) and presbyope (>45 years, 2 subjects). The results of Mann-Whitney U-test tests do not show statistically significant differences based on refractive error or age in any of the two tasks ($p > .05$ in all comparisons). Therefore, in our groups of subjects, the refractive error is a statistical variable that does not influence the results.

Biomedical Optics EXPRESS

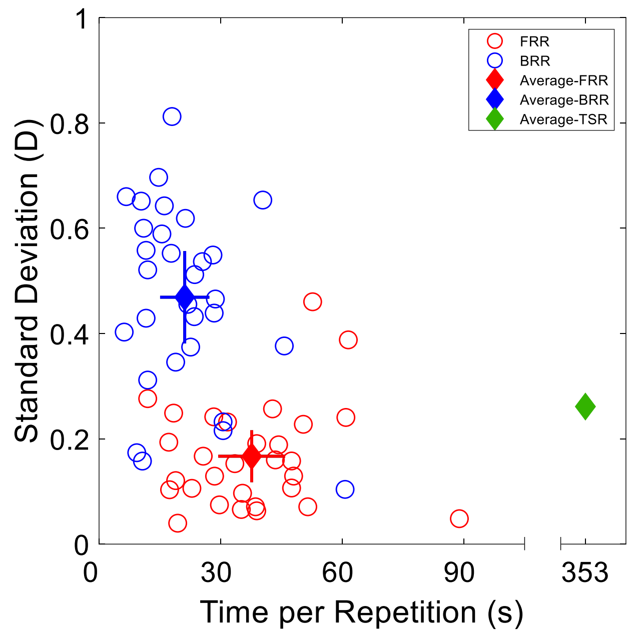

Fig. 7. Precision and time to perform the tasks. Standard deviation across repetitions vs the time per repetition for flicker-minimization (red), blur-minimization (blue), and Traditional Subjective Refraction (TSR, green). For TSR, the standard deviation and the average time is extracted from the literature [18]. The filled diamonds indicate the average across subjects.

4. Discussion

4.1. Perceptual and accommodative consequences of chromatic defocus flicker

In this study, we have measured the perception of periodic changes in defocus using a chromatic stimulus made of blue and red components, in the extremes of the Longitudinal Chromatic Aberration (LCA) of the eye. In Experiment 1, with free accommodation, we have shown that the average result across subjects for the unsupervised flicker-minimization task is -0.33 D with respect to the baseline (considered to be the far refraction of the subjects), takes 38 seconds per repetition and is very repeatable (±0.17 D). Although the average result across subjects for the unsupervised blur-minimization task is -0.12 D, closer to the baseline, and is faster, 21 seconds per repetition, the repeatability is very low (±0.47 D). These results suggest that the unsupervised flicker-minimization task is more reliable than the unsupervised blur-detection task, and still fast.

Accommodation is a potential cause of variability and systematic shifts during any subjective (or objective) measurement, and these experiments do not elude it. However, to study the effect of accommodation in the flicker-minimization and blur-minimization tasks, we replicated the same experimental procedure but with the accommodation paralyzed (in Experiment 2). In Fig. 4 and Fig. 6(B) we showed that, for this pool of young subjects, there is no statistical difference in the outcome for the flicker-detection task comparing the results of Experiment 1 (free accommodation) and Experiment 2 (paralyzed accommodation). Paralyzing accommodation also had the effect of reducing the measurement variability to its lowest value (±0.15 D on average; in the flicker-minimization). However, we found a small myopic offset (-0.33 D) from the best far refraction of the subjects in the flicker-minimization task, that could still be attributed to a small remaining residual accommodation (tonic accommodation). Being stable and largely

Biomedical Optics EXPRESS

unaffected by the stimulus, we could refer to this accommodative state as the 'resting position' of the eye, in a 'dark focus' of 'tonic accommodation' closer than infinity, previously reported in conditions where the accommodation is lost, for example in night myopia, or due to lags/leads of accommodation [5,22,23]. These results confirm that the accommodation barely influences the result of the flicker-minimization task. Although promising, these findings should be confirmed in a higher number of subjects.

Furthermore, we included different starting points in the different repetitions, simulating different amounts of myopia or hyperopia in the same subject. We found that the blur-minimization task is undoubtedly affected by dynamic accommodation. In contrast to the Traditional Subjective Refraction (TSR) procedure used in clinics, which implements different strategies (such as the fogging technique) to reduce the impact of accommodation and reach the center of the depth of focus interval, this task, which is unsupervised, is not protected and results in important variabilities due to offsets that depend on the starting point: + 0.23 D if the starting point is myopic, and -0.53 D if it is hyperopic (Fig. 6(A)). Hyperopic starting points can be accommodated (red points in Fig. 3(A) and Fig. 3(C)), bringing the image into focus and finishing the staircase prematurely, leaving a negative offset (underestimating the correction). Similarly, depth of focus produces positive shifts in myopic defocus because subjects judge the image sharply before reaching the maximum optical quality and stop the staircase fractions of a diopter in front of the best focus (blue points in Fig. 3(B) and Fig. 3(D)).

As seen in the examples in Fig. 3, the flicker-minimization task forces the subject to reach the best focus and the staircases oscillate on both sides of it, removing the positive offset associated with hyperopic starting points. Figures 6(A) and 6(B) suggest that, at the same time, the accommodation mechanism is to a large extent deactivated during the flicker-minimization task. Defocus is present in the stimulus during this task, as in blur-minimization, and is certainly perceived by the subject, but it is not part of the flicker-minimization task. We hypothesize that the accommodation of the eye remains fixed because the fast change induced by the TDW prevents its activation. Other studies have shown that accommodation varies as much as 0.5 D with flickering light at relevant frequencies for this study (between 10 and 20 Hz) in monochromatic stimuli [24,–26] and chromatic stimuli [27]. However, there are substantial differences in the methodologies of those studies. On the one side, the task of the subjects was to fixate on the stimulus and therefore elicit on purpose the accommodation response. In the defocus flicker-minimization task, flicker is the main cue and accommodation should not be elicited. On the other hand, these studies used stimuli flickering in luminance, not in defocus. Several studies have shown that accommodation is not able to follow changes faster than 2 Hz [7–12]. In particular, Walsh et al. [11] tested the threshold to defocus changes, but mechanical limitations only allowed temporal frequencies up to 4 Hz and they did not find any influence of accommodation. We have shown indirectly with two procedures (paralyzing accommodation and including hyperopic and myopic repetitions) that the fast defocus alternation in the image does not provide a fixed reference to focus and thus does not elicit accommodation. Nevertheless, future studies will address direct measurements of the accommodative response in defocus flicker tasks.

4.2. Offset in the outcome of the flicker-minimization task

Accommodation to the stimulus can be discarded as an explanation for the offset found in the flicker-minimization task, but several other reasons could provide a plausible explanation. For example, the flicker-minimization task contains the implicit assumption that the best retinal focus lies in the intermediate position (in diopters) between the red focus and the blue focus (Fig. 1). Therefore, changes in the spectral composition of the stimulus (spectral width and position of the red and blue peaks) could shift the residual refraction measured with the flicker-minimization task. Besides, the relationship between wavelength and focus position in diopters (the LCA curve) is not lineal [28,29], and the monochromatic wavelength-in-focus for subjective refraction changes with the subject [30], predicting the polychromatic spherical equivalent from monochromatic measurements difficult to model [31]. Furthermore, even the gold standard, the polychromatic spherical equivalent measured with the TSR, can change with the color temperature of the white light used. Moreover, the variability of any subjective measurement is extremely related to the subjective depth of focus, not only for optical reasons (aberrations) but for neuronal reasons [32].

Instrument myopia (an effect also related to accommodation), pupil size effects due to relatively low ambient light levels during the measurements, such as potential focus shifts due to spherical aberration or depth of focus increments, or accommodation lag could also be blamed for this small but significant offset between found in the flicker-minimization task. The magnitude of most of the mentioned effects, separately, could be higher than the offset found in our measurements [30,–33]. The calibration of the instrument and the fidelity of the TDW to the nominal power, as well as the distances involved in the optical set-up, were checked before the measurements, and the potential deviations in optical power could be considered negligible [34]. Still, further research of all these hypotheses under clinical conditions in a large number of subjects will allow the development of strategies to null or compensate for the offset.

4.3. Novel application of fast changes in defocus: The Direct Subjective Refraction

In this study, we have developed a paradigm using tunable lenses to measure the minimum flicker perception to defocus changes using a chromatic stimulus. In fact, the outcome of this task can be considered as a residual refraction (only the spherical equivalent component though) of the refractive error of the eye (see Fig. 1). In this paradigm, the task of the observer is to minimize (1) the flicker in the stimulus and (2) the color distortions. Both perceptual effects are dynamic, concurrent, and very apparent to the observer. As a result, the two perceptual effects used in the minimization task reinforce each other to converge to a common focus, making the task easy for the observer. Around the focus, flicker and color distortions are image features perceptually stronger than the static blur commonly used to guide the TSR. Besides, the different chromatic effects depending on the position of the TDW with respect to the retinal plane (myopic or hyperopic) also provide a cue for the direction of focus, not present in the blur-minimization task. In other words, the dual minimization task is more sensitive than the one used in the TSR method (blur minimization) and less affected by accommodation.

The TSR procedure is ubiquitous in eye care clinics. Despite being cumbersome and time-consuming on some occasions, it has not advanced much in decades. Some technologies such as automated phoropters have made the procedure easier but have not improved significantly the methodology [18]. Objective refractors, as wavefront autorefractors, now provide good approximations to TSR but have not been able to replace it [35,36].

Subjective visual tasks are inherently slow, they entail a large series of trials, each one requiring a perceptual judgment from the observer (blur minimization, blur preference, or letter identification in the case of subjective refraction) and a decision by the practitioner. TSR begins by displacing the starting point far away from the best prior estimation available, usually provided by objective refraction (or sometimes by a lensometer), to the myopic side. This long detour in the through-focus trajectory (fogging), is inefficient in terms of trials, but allows to deal with accommodation, and also provides the direction of focus. An ideal method to measure the subjective refraction would provide a shortcut toward the final spherical equivalent of the patient, using the lowest number of perceptual judgments: only a few steps separating the patient's subjective focus from the one measured objectively.

Subjective visual tasks, such as subjective refraction, are inherently slow and require multiple trials, each one requiring a perceptual judgment from the observer and a decision of the practitioner. Traditional subjective refraction typically starts with a far-off starting point from the best prior estimation available, usually provided by objective refraction. An ideal method would provide a

Biomedical Optics EXPRESS

shortcut to the final prescription, requiring fewer perceptual judgments and steps to get there, while also accounting for accommodation and direction of focus.

Our paradigm can be used to measure the spherical equivalent of the refractive error of an eye, which disentangles, to a large extent, the accommodation mechanism and provides the patient with a visual hint of the direction of focus. The starting point can be the best estimation provided by objective refraction, and the spherical equivalent can be found directly. The number of trials (perceptual judgments) is reduced, and each one is straightforward and not supervised, producing faster measurement times than the TSR (Fig. 7). We named this methodology the Direct Subjective Refraction (DSR) method. The DSR task is direct in the sense that color provides an unambiguous cue for the direction of the next step in the staircase (color distortions are different on both sides of the retina: blueish on the myopic side, and reddish on the hyperopic side).

In the last steps of the TSR, the practitioner checks whether power changes of ±0.25 D improve the visual acuity or visual comfort, sometimes using colored backgrounds (such as the duochrome test). These final checks inspired the development of the DSR method. This paradigm performs 15 of those optical power changes per second, during the duration of the measurement and in every step of the subjective staircase leading to the spherical equivalent. Besides, 15 Hz is a frequency providing maximum temporal sensitivity to flicker [14,15], and therefore optimal for the task, although out of reach for the accommodative system. Hence, DSR provides a much stronger perceptual cue (in fact two concurrent and reinforcing signals: flicker and color) than TSR and is isolated from accommodation (because blur, the main clue for the accommodative system is no longer involved in the task), allowing straightforward measurements for the patients without requiring the guidance of the clinician. Our results show that this flicker-minimization paradigm provides a precise, accurate, and fast estimation of the residual spherical equivalent.

The ideal method to evaluate the refractive error would provide a good balance between measurement time and variability. The fogging techniques required to reduce the influence of accommodation make TSR tiresome for the subject and the practitioner and increase the measurement time. TSR is indeed a time-consuming procedure, reported to take 6 minutes per subject, on average [18]. An unsupervised version of the traditional procedure, like the blur-minimization task performed in this study, is very quick, taking about 21 seconds per repetition. However, it has low precision, with repeatability across subjects of ±0.47 D, and systematic deviations that depend on the starting point. The DSR method, insensitive to accommodation by design, does not require fogging strategies. It is not only a very precise (±0.17 D) and accurate procedure (-0.33 D without offset compensation) but also fast: it takes less than 40 seconds to be performed, on average. The fastest subject took only 12 s per repetition, and the slowest, 90 s. The short measurement time (plus only 1.5 minutes of explanation) allows thorough training and would allow several repetitions, although only a few are needed (probably two, one for training and approximation and another one for refinement), given the high repeatability of the method. An assessment of the reliability of Experiment 1 supports these conclusions, as it reports a Cronbach's Alpha value of 0.979 -with a reliability factor of 0.95- estimates that only the first 4 repetitions are not redundant.

However, the current paradigm has important limitations. In this study, we have only measured the spherical equivalent, but not the amount of astigmatism in the subjective correction. Moreover, we measured the subjects with their usual corrections on, therefore reducing the amount of astigmatism, if present, to a residual value. Pilot experiments have shown that the DSR task can be performed in presence of astigmatism [37], at least up to one diopter but presumably more. This promising result suggests that the DSR approach described could also have the potential for fast and unsupervised measurement of subjective refraction including astigmatism. For that, the current method should be refined with new stimuli, oriented features, and new measurement protocols considering flicker and chromatic distortions in different orientations.

Biomedical Optics EXPRESS

Another limitation of the study is the sample of the population measured. All of them had normal vision, no cataracts, no history of eye surgery, amblyopia, or any other eye disease, most of the subjects were young subjects, and the proportion of hyperopes, which can be more affected by accommodation, was low (only 12%). Besides, there are subjects with color vision deficiency, where the absence or lack of functioning of one or more types of photoreceptors prevents from discrimination of colors. In the DSR method, the chromatic component is crucial as a cue for the direction of defocus, and therefore it could be difficult to perform for subjects with these color deficiencies. However, we hypothesize that, because the LCA is a consequence of the optics of the eye, not depending on the perception, and the chromatic elements of our stimuli are spatially separated, they will experience flicker in different regions of the stimulus (corresponding to different chromatic elements) that depends on the position of the TDW with respect to their retina. In summary, different parts of the stimulus will flicker depending on the position of the TDW, and therefore these subjects will be able to perform the DSR task. In any case, including a higher and more diverse sample size will help to overcome this limitation.

5. Conclusions

A temporal defocus wave (fast and periodic changes in defocus) of 0.25 D of amplitude and 15 Hz of frequency produces a strong flicker perception that depends on the overall defocus of the retina and that is minimum when the eye is in focus. Chromatic stimuli interact with the temporal defocus wave and the longitudinal chromatic aberration of the eye to produce chromatic distortions that provide an extra perceptual cue for the direction of focus: a bluish tint when the defocus is myopic and a reddish tint when hyperopic. With those strong cues, the task of self-focussing the eye by minimizing flicker and chromatic distortions is easy, highly repeatable, and fast. Most importantly, chromatic defocus flicker seems to deactivate the accommodative response of the visual system, making the measurement insensitive to any myopic or hyperopic origin, and therefore the flicker-minimization task is barely affected by accommodation. This study illustrates the possibility of using the chromatic flicker-minimization task in the development of new methods for estimating the refractive error of an eye with the potential of providing fast and accurate unsupervised subjective measurements of the refraction.

Funding. "la Caixa" Foundation (ID 100010434; LCF/BQ/DR19/11740032); Ministerio de Educación y Formación Profesional (FPU17/02760); Ministerio de Ciencia, Innovación y Universidades (FIS2017-84753-R, ISCIII DTS2016/00127).

Acknowledgments. We thank Manuel Rodriguez-Vallejo and Nuria Garzon for useful feedback on previous versions of the manuscript. We sincerely appreciate the valuable comments and suggestions of the reviewers, which helped us in improving the quality of the manuscript.

Disclosures. A patent application on the Direct Subjective Refraction procedure has been filed by the Institute of Optics (CSIC) with C.D. and V.R.L. as inventors.

Data Availability. Data underlying the results presented in this paper are not publicly available at this time but may be obtained from the authors upon reasonable request.

References

1. D. B. Elliott, "Clinical Procedures in Primary Eye Care, 3rd edition," Clin. Exp. Optom. **91**(5), 496–497 (2008).
2. A. Ohlendorf, A. Leube, and S. Wahl, "Steps towards amarter solutions in optometry and ophthalmology—Inter-device agreement of subjective methods to assess the refractive errors of the eye," Healthcare **4**(3), 41 (2016).
3. A. P. Venkataraman, D. Sirak, R. Brautaset, and A. Dominguez-Vicent, "Evaluation of the performance of algorithm-based methods for subjective refraction," J. Clin. Med. **9**(10), 3144–3148 (2020).
4. C. Dorronsoro, A. Radhakrishnan, J. R. Alonso-Sanz, D. Pascual, M. Velasco-Ocana, P. Perez-Merino, and S. Marcos, "Portable simultaneous vision device to simulate multifocal corrections," Optica **3**(8), 918 (2016).
5. W. N. Charman, "The eye in focus: Accommodation and presbyopia," Clin. Exp. Optom. **91**(3), 207–225 (2008).
6. W. J. Hament, V. A. Nabar, and R. M. M. A. Nuijts, "Repeatability and validity of Zywave aberrometer measurements," J. Cataract Refract. Surg. **28**(12), 2135–2141 (2002).
7. F. W. Campbell and G. Westheimer, "Sensitivity of the eye to differences in focus," J. Physiol. **143**, 18P (1958).

Biomedical Optics EXPRESS

8. F. W. Campbell, J. G. Robson, and G. Westheimer, “Fluctuations of accommodation under steady viewing conditions,” J. Physiol. **145**(3), 579–594 (1959).
9. V. V. Krishnan, S. Phillips, and L. Stark, “Frequency analysis of accommodation, accommodative vergence and disparity vergence,” Vision Res. **13**(8), 1545–1554 (1973).
10. F. Sun, L. Stark, A. N. Nguyen, J. Wong, V. Lakshminaryanan, and E. Mueller, “Changes in Accommodation with Age: Static and Dynamic,” Optom. Vis. Sci **65**(6), 492–498 (1988).
11. G. Walsh and W. N. Charman, “Visual sensitivity to temporal change in focus and its relevance to the accommodation response,” Vision Res. **28**(11), 1207–1221 (1988).
12. S. Mathews and P. B. Kruger, “Spatiotemporal transfer function of human accommodation,” Vision Res. **34**(15), 1965–1980 (1994).
13. N. Sharmin and B. Vohnsen, “Monocular accommodation response to random defocus changes induced by a tuneable lens,” Vision Res. **165**, 45–53 (2019).
14. C. Dorronsoro, V. Rodríguez-Lopez, X. Barcala, E. Gambra, V. Akondi, L. Sawides, Y. Marrakchi, E. Lage, W. S. Geisler, and S. Marcos, “Perceptual and physical limits to temporal multiplexing simulation of multifocal corrections,” Invest. Ophthalmol. Vis. Sci. **60**, 6465 (2019).
15. V. Rodriguez-Lopez, W. S. Geisler, and C. Dorronsoro, “The spatiotemporal defocus sensitivity function [Manuscript submitted for publication],” (2023).
16. D. B. Elliott, *Clinical Procedures in Primary Eye Care*, 4th ed. (2014).
17. D. B. Elliott, “What is the appropriate gold standard test for refractive error?” Ophthalmic Physiol. Opt. **37**(2), 115–117 (2017).
18. V. Rodriguez-Lopez and C. Dorronsoro, “Beyond traditional subjective refraction,” Curr. Opin. Ophthalmol. **33**(3), 228–234 (2022).
19. C. Dorronsoro and V. Rodriguez-Lopez, “Device and system to conduct optometric measurements and method to adjust the optical power of a tunable lens. OEPM Patent Application Number: 201930198,” U.S. patent 201930198 (n.d.).
20. A. Radhakrishnan, D. Pascual, S. Marcos, and C. Dorronsoro, “Vision with different presbyopia corrections simulated with a portable binocular visual simulator,” PLoS One **14**(8), e0221144 (2019).
21. D. H. Brainard, “The Psychophysics Toolbox,” Spat. Vis. **10**(4), 433–436 (1997).
22. J. M. Otero, “Influence of the state of accommodation on the visual performance of the human eye,” J. Opt. Soc. Am. **41**(12), 942–948 (1951).
23. P. Artal, C. Schwarz, and C. Ca, “Night myopia studied with an adaptive optics visual analyzer,” PLoS One **7**(7), e40239 (2012).
24. C. Neary, “The effect of high frequency flicker on accommodation,” Ophthalmic Physiol. Opt. **9**(4), 440–446 (1989).
25. D. I. Flitcroft, “Accommodation and flicker: evidence of a role for temporal cues in accommodation control?” Ophthalmic Physiol. Opt. **11**(1), 81–90 (1991).
26. C. a. Charman, “Accommodation responses to flickering stimuli,” Ophthalmic Physiol. Opt. **16**(5), 391–408 (1996).
27. L. Zhang, D. Guo, C. Xie, Y. Wen, X. Zhang, L. Jin, J. Tong, and Y. Shen, “The effects of colour and temporal frequency of flickering light on variability of the accommodation response in emmetropes and myopes,” BMC Ophthalmol. **21**(1), 88 (2021).
28. R. E. Bedford and G. Wyszecki, “Axial Chromatic aberration of the human eye,” J. Opt. Soc. Am. **47**, 564_1–565 (1957).
29. M. Vinas, C. Dorronsoro, D. Cortes, D. Pascual, and S. Marcos, “Longitudinal chromatic aberration of the human eye in the visible and near infrared from wavefront sensing, double-pass and psychophysics,” Biomed. Opt. Express **6**(3), 948–962 (2015).
30. C. Coe, A. Bradley, and L. Thibos, “Polychromatic refractive error from monochromatic wavefront aberrometry,” Optom. Vis. Sci. **91**(10), 1167–1174 (2014).
31. L. N. Thibos, “Unresolved issues in the prediction of subjective refraction from wavefront aberration maps,” J. Refract. Surg. **20**(5), 533–536 (2004).
32. A. Leube, T. Schilling, A. Ohlendorf, D. Kern, A. G. Ochakovski, D. Fischer, and S. Wahl, “Individual neural transfer function affects the prediction of subjective depth of focus,” Sci. Rep. **8**(1), 1919 (2018).
33. V. Labhishetty, S. A. Cholewiak, A. Roorda, and M. S. Banks, “Lags and leads of accommodation in humans: Fact or fiction?” J. Vis. **21**(3), 21 (2021).
34. C. Dorronsoro, X. Barcala, E. Gambra, V. Akondi, L. Sawides, Y. Marrakchi, V. Rodriguez-Lopez, C. Benedi-Garcia, M. Vinas, E. Lage, and S. Marcos, “Tunable lenses: Dynamic characterization and fine-tuned control for high-speed applications,” Opt. Express **27**(3), 2085–2100 (2019).
35. J. K. Sun, H. Qin, L. P. Aiello, M. Melia, R. W. Beck, C. M. Andreoli, P. A. Edwards, A. R. Glassman, and M. R. Pavlica, “Evaluation of visual acuity measurements after autorefraction vs manual refraction in eyes with and without diabetic macular edema,” Arch. Ophthalmol. **130**(4), 470–479 (2012).
36. F. Segura, A. Sanchez-Cano, C. Lopez de la Fuente, L. Fuentes-Broto, and I. Pinilla, “Evaluation of patient visual comfort and repeatability of refractive values in non-presbyopic healthy eyes,” Int. J. Ophthalmol. **8**(5), 1031–1036 (2015).
37. V. Rodriguez-Lopez and C. Dorronsoro, “Direct subjective refraction with temporal defocus waves,” Invest. Ophthalmol. Vis. Sci. **60**, 4265 (2019).